The Race for the Double Helix—providence and personalities

Dr Francis Crick and Professor James Watson discuss their Nobel Prize achievement, in discovering the genetic function of DNA. The commentary is by Professor Sir Michael Swann, chairman of the Governors of the BBC.

FRANCIS CRICK: Why does a calf look like its mother, or, for that matter, why do cows always produce calves and not rabbits? The scientist wants to know the details of the process of inheritance. We know that one sperm from a bull is enough to fertilise a cow and produce a new individual, with four legs, a head, all the details right, and different from any other cow. All that information (or, at least, half of it) has to be contained in the minute head of this very tiny sperm. That shows that it must be written in a very minute language, a chemical language. Not only that: when the egg has been fertilised, it produces millions of cells. In each one of those cells there's a precise copy of all that genetic information. When I left physics 25 years ago it seemed to me that these two problems, how genetic information is stored in such a small space, and how it is copied exactly, were the most important problems in biology.

MICHAEL SWANN: A young American, James Watson from Harvard, and two Englishmen, Francis Crick from Cambridge and Maurice Wilkins from London, were awarded the 1962 Nobel Prize for Medicine. They discovered the nature of the inheritance chemical—DNA—deoxyribonucleic acid. But before the moment of elation, there were blunders, frustration, conflicts.

Cambridge in the early 1950s was the setting for Watson and Crick's part in the DNA story. After the war, this was a rather exciting place: a lot of us, young and not so young, had come back to do biological research. I myself was doing cell biology. There was a lot of interest in the chemistry of life, and foremost amongst the characters around the place were Francis Crick and Jim Watson.

Crick was already about 35 and he hadn't even finished his own doctoral thesis, though I remember he was remarkably good at giving advice to other people on solving their doctoral theses. Watson was a very bright young American who hadn't done a great deal. Crick was a physicist: he didn't know much about biology, and Watson didn't know much about molecules.

What is it in living cells that carries the genetic information? What specifies how an organism grows? At one level, chromosomes are the answer, and within the chromosomes, the genes. But how does a gene work and what is it made of? By the end of the 1940s, it was becoming clear that DNA was the most likely candidate. Professor John Randall had set up a group at King's College, London, to investigate the processes in living cells. A member of this group was Maurice Wilkins.

MAURICE WILKINS: I was a physicist who had worked during the war on the atom bomb. I was rather disgusted by the way in which science was being misapplied, and so I wanted to get out of physics. There were bigger potentialities for using science in a beneficial way in biology.

MICHAEL SWANN: Wilkins's work on genetic material took him on a visit to Naples early in 1951. While there, he gave a talk on DNA. In the audience was Jim Watson.

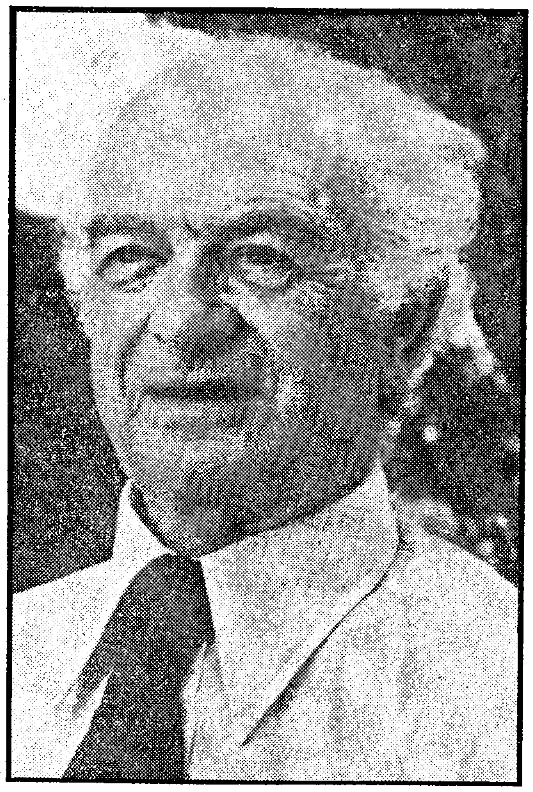
JAMES WATSON: I suddenly became aware that there existed somebody who was trying to solve the structure of DNA, which seemed to be a likely candidate for the gene. Maurice was deadly serious, and I tried to talk to him, but he's English, he doesn't talk much with strangers. It wasn't an obvious coming together of like minds.

MICHAEL SWANN: Jim Watson realised that England was the ideal place to pursue his DNA interest. By a lucky accident, he managed to obtain a place at Cambridge.

JAMES WATSON: My first couple of months in Cambridge were terribly chaotic. I went to a dismal place with a landlady who wanted me to take off my shoes when I came in at night, and didn't want me to flush the toilet after ten in the evening. None of these things bothered me because I'd met Francis, and it was a tremendous change. Before then, I had been with lots of bright people, but I couldn't agree with any of them. Our thoughts were somewhat dominated by Linus Pauling, because he was the great chemist who was going to solve biology.

FRANCIS CRICK: Had you met Linus?

JAMES WATSON: He smiled at me. We were in the washroom of the Athenaeum, the faculty club of Caltech, and Linus looks down at me and smiles. I think it's a strange place for this to happen.



Linus Pauling: he caught a cold

MICHAEL SWANN: Linus Pauling, then Professor of Chemistry at the California Institute of Technology, is one of the most eminent chemists of this century. He was awarded the Nobel Prize for his work on the chemical bond. He came to public notice recently, through his suggestion that vitamin C could fend off the common cold. In the late 1940s, brilliant insight enabled Pauling to work out an element in the structure of proteins—the alpha helix.

LINUS PAULING: One day, when I was the Eastman Professor at Oxford in the Spring of 1948, I caught a cold—it was before the vitamin C days—and, after a day or two in bed, reading science fiction, I got tired of that and I thought: why don't I discover the alpha helix? I took a piece of paper and I drew on it a representation of an extended polypeptide chain with the distances approximately right and the angles right, except for one. So I folded the paper and, finally, I found a way, by folding the paper, to make this bond angle have the value 110 degrees. I finally found a way of folding, such that a hydrogen bond held the helical structure together and had just the right dimensions.

FRANCIS CRICK: Linus Pauling was a genius at this sort of thing. He was capable of taking short cuts. What we decided was that we'd try and use the same method.

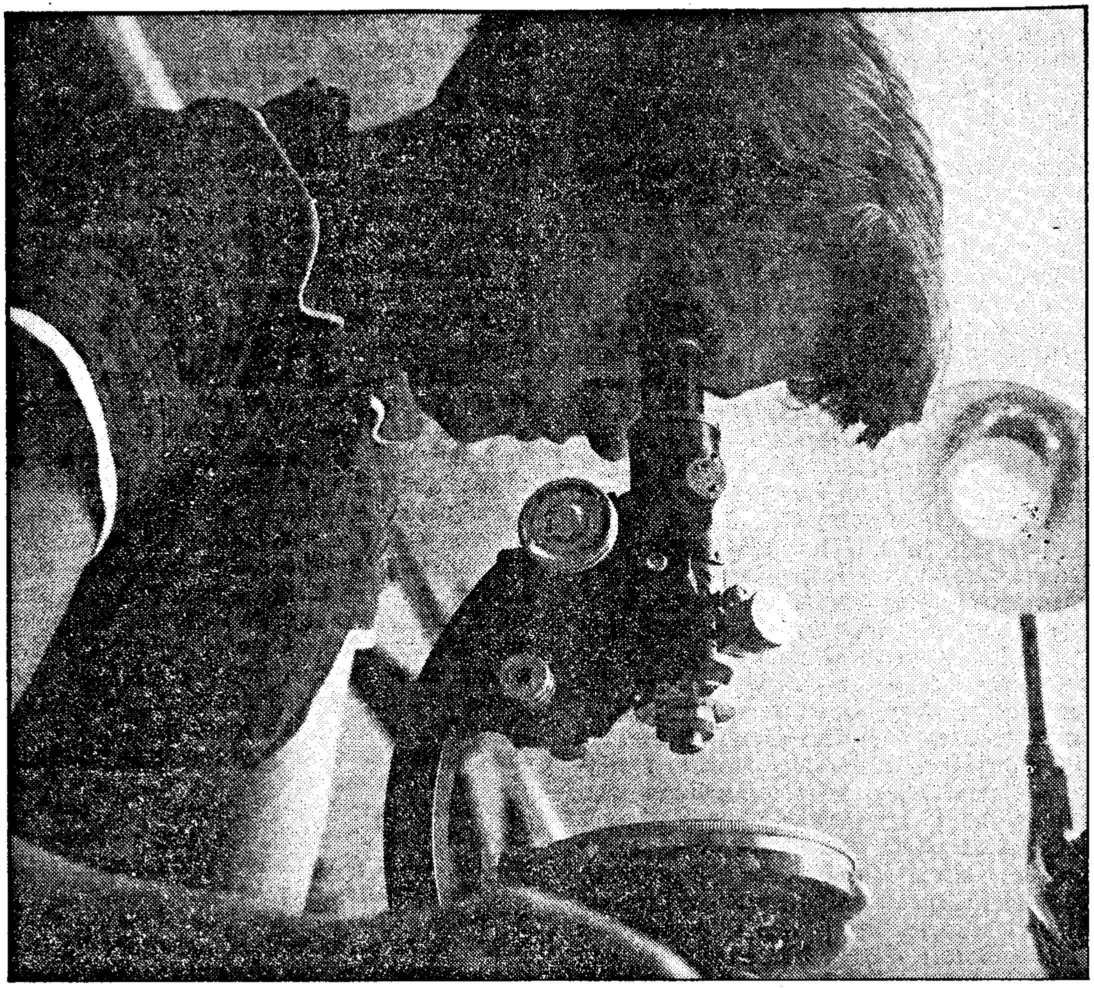
MICHAEL SWANN: It was known that there were hundreds of sub-units in the DNA molecules, so that there were undoubtedly millions of possible combinations, and one needed to know which was the right one. One needed some hard experimental data on DNA, and the only place where that was coming from at the time was King's College, London.

RAYMOND GOSLING: Professor Randall was using an electron microscope to look for the genetic structure in ram sperm. As a junior research student at the time, I was given the job of persuading a whole heap of ram's sperm to lie down in an orderly fashion and try to get a diffraction photograph of them. Not getting a very clear picture, I went to Maurice Wilkins, who was looking at extracted DNA, and he had found that you could pull it into fibres. I used these fibres to make a specimen to give me a DNA pattern that I could compare with the ram's sperm pattern. With the original camera, we had a fairly weak X-ray beam. We wanted a much more intense beam that would let us look at single DNA fibres. An X-ray set had just been developed that enabled us to get diffraction photographs from a small crystalline region within one single fibre.

MICHAEL SWANN: Deciding what these pictures said about DNA's structure needed the special expertise which Rosalind Franklin brought to the King's College group.

AARON KLUG: I first met Rosalind Franklin in late 1953 at Birkbeck College, where we both came to work on problems of virus structure. I was, perhaps, her closest and certainly her last scientific colleague until her death four years later. Within a short time of her arrival at King's, she got excellent clear pictures which could be used for quantitative analysis.

MICHAEL SWANN: Scientifically, the King's



HENRY GRANT

Rosalind Franklin: prepared to discount Crick and Watson as serious competitors

College work was going well, but personal relationships between Rosalind and Maurice Wilkins had become rather strained.

FRANCIS CRICK: Rosalind Franklin was a professional crystallographer and I think she regarded Maurice as being less so.

JAMES WATSON: It was in the days before Women's Lib—which, she felt, was long overdue. Women were badly discriminated against, certainly in King's College. I think Maurice, when he brought Rosalind in, afterwards regretted he'd given away his problem.

MAURICE WILKINS: I was a general physical molecular biologist, and I hadn't specialised in X-ray diffraction methods. Rosalind Franklin was brought into this work because she was experienced and a specialist. If you regard getting the structure of DNA as a race, we lost very early on, because we didn't find it possible to work together.

RAYMOND GOSLING: Maurice was a reserved person. Rosalind was intense, and so they were about as different as you could get.

FRANCIS CRICK: But how did *you* get on with Rosalind?

JAMES WATSON: Terrible.

FRANCIS CRICK: She didn't think you knew much crystallography.

JAMES WATSON: She was totally correct.

MAURICE WILKINS: Rosalind was rather prepared to discount Crick and Watson as being very serious competitors. There was a general impression that they were like butterflies; they were flitting around with lots of brilliance but not much solidity. Obviously, this was a ghastly misjudgment.

MICHAEL SWANN: When Rosalind Franklin's pictures were good enough to analyse, she presented her results at a meeting in 1951.

JAMES WATSON: It was in King's, next to Somerset House. It was a very old place, almost Dickens-like. Not many people really cared about what Rosalind said. It was a small audience. I made a terrible mistake—

FRANCIS CRICK: Being a new boy in crystallography, how were you to know the difference between a unit cell and the asymmetric unit?

JAMES WATSON: So I got water wrong, by a factor of 24 or something.

FRANCIS CRICK: When Jim reported what she said, it seemed that it was a dry structure. Actually, the facts were that it was extremely wet; this was due to the misunderstanding of two technical terms. So we had an abortive attempt trying to solve the structure as if it were dry. We even went so far as to build models.

JAMES WATSON: We called up the people at King's and said we had solved it. They came up, scared to death that we might have, and probably also sceptical. Rosalind didn't really think this was going to work. When we started explaining things, she immediately asked: 'Where is the water?' I said: 'There wasn't any. *You* said that.' And, of course, she said: 'I didn't say that.' I felt rather stupid.

MAURICE WILKINS: The Cambridge model really was an embarrassment to us. To see these highly intelligent Cambridge chaps turning up something crazily wrong. The whole thing was inside-out.

JAMES WATSON: It had the effect of crying 'Wolf!'. Up to then, if we asked them for some data, they would tell us.

MICHAEL SWANN: The fiasco over the model irritated Sir Lawrence Bragg, who was the head of the Cavendish Laboratory. Crick didn't endear himself to Bragg. I remember Bragg once saying to me that Crick's extremely penetrating voice made his head buzz. This last trouble wasn't the only one, because, some months earlier, there'd been a problem over scientific priority.

JAMES WATSON: As far as I could tell, Francis had told the Professor he'd stolen his ideas. Bragg told me afterwards he didn't want to go to the tea-room because he'd have to hear Francis's voice. It would remind him of this thing. From then on, although Bragg had a lot of ambitions, chiefly about proteins, one of his minor ambitions was that Francis should leave the lab.

MICHAEL SWANN: Bragg wanted Crick to stop talking so much and get on with his PhD thesis, and so he actually ordered Francis to stop working on DNA. Bragg and Randall were two very powerful and important figures. You might say they'd really carved up the territory between themselves, because Bragg's lab at Cambridge, it was agreed, would work on proteins and Randall's lab in London, it was agreed, would work on DNA. Protocol in those days (and even today, as a matter of fact) is really rather important. But, of course, those sorts of restraint didn't apply to Linus Pauling.

JAMES WATSON: In fact, Linus wrote me a letter which said that he was going to come to Europe and hoped he could talk to me about our work on DNA. Pauling really was interested in everything. We kept telling Maurice this.

FRANCIS CRICK: Yes, we kept trying to frighten him, like the mothers in the time of Napoleon who used to try and send their children to sleep by saying: 'If you don't go to sleep, Boney will come.' We used to say to Maurice: 'If you don't solve the structure, Linus Pauling will solve it.' But Maurice wanted to do it the sound way, not be bullied by us.

JAMES WATSON: Maurice had told us that Linus had asked him for the X-ray photographs. I think Maurice thought: 'I don't want to send Linus our data until we've had enough time ourselves to look at it.'

LINUS PAULING: I wrote to Wilkins at King's College, asking if I could have prints of the photographs that he had obtained, but my effort was not successful. I continued to work on the basis of poorer photographs, and this was in part responsible for my failure to find the structure.

MICHAEL SWANN: At the time Linus Pauling wanted to come to England, the McCarthy purges were at their height in America. Because of Pauling's pacifist sympathies, his passport was withdrawn. Some news of Linus's progress reached the Cavendish through his son, Peter.

PETER PAULING: My father wrote me a letter saying that he had an idea for the structure of DNA and was going to publish it in the Proceedings of the National Academy of Sciences. He asked me whether I wanted a manuscript copy of it.

JAMES WATSON: Of course, we were upset.

The question was: could it be right? We knew that Linus didn't have a good X-ray photograph. So could he have thought it through without any of the King's data?

PETER PAULING: In those days, I had no idea what a gene was, no idea what DNA was. This paper came, and I didn't know what any of it meant. I gave it to Jim Watson and Francis Crick. According to Jim, not only did I not know what nucleic acids were, but my father didn't know either.

JAMES WATSON: He had decided that DNA, which is deoxyribonucleic acid, wasn't, in fact, an acid. I rushed around Cambridge showing it to people, asking could it be right? And they all said, no, it's an acid. As the afternoon wore on, we had a feeling of great relief: we still had a chance, the problem hadn't been solved by Linus.

FRANCIS CRICK: More than great relief, Jim. We were hilarious, I'm sorry to say. Linus had bad luck. He had poor X-ray pictures but, even worse than that, they were misleading. They were really two X-ray pictures on top of one another. It isn't surprising he got it wrong. Now at King's, they had much better X-ray pictures. An X-ray picture is not a simple picture like a photograph: to understand what you expect from a helix, you have to work out a mathematical theory which shows you what the diffraction pattern would be. When Jim went to King's with the erroneous structure of Linus Pauling in his pocket, he was familiar with the X-ray diffraction theory.

JAMES WATSON: Maurice read it and, in his usual way, didn't convey much enthusiasm one way or the other, but I guess he said he didn't think Linus was trying to get the right structure. At the same time, however, he let loose the bombshell, at least to me, that actually there were two types of DNA X-ray photographs: there was the form which I knew about, called the A form, which gave the crystalline pattern, but also a second form called the B form. He opened a drawer and took out a photograph and, boy! I could hardly believe it. It was a perfect helix. So I said: 'Maurice, you got to build models.' But the trouble was Miss Franklin. So I thought I should go over and see Rosalind. I went in and told her I had a copy of the Pauling manuscript, if she would like to see it. It was clear that she was annoyed at my trying to tell her something about crystallography. She came toward me. I thought she was going to hit me. So I quickly got out, at which point Maurice was coming around, and she almost hit Maurice.

MAURICE WILKINS: Who hit who? I don't think anybody hit anybody. Actually, some people may have thought someone was going to hit someone. There certainly weren't very friendly feelings.

MICHAEL SWANN: By now, Lawrence Bragg had heard of Linus Pauling's attempts. Now Bragg wanted DNA to be a British success, so he agreed that Jim Watson could start working on DNA again. To represent the structure, it was necessary to build models.

FRANCIS CRICK: We used balls to represent atoms and rods to represent the bonds between atoms. There is a very large number of ways, given the chemical formula, that you can build the model.

JAMES WATSON: I would do it, maybe, three hours a day. It's awfully hard to give up an idea of your own, so I started putting the phosphates in the centre—maybe because it was like a Pauling structure. Francis wasn't comfortable on this and asked me why not try putting the phosphates on the outside.

AARON KLUG: Francis may have been playing the devil's advocate in telling Jim to try the phosphates on the outside, but, indeed, there were very good reasons for doing so. Rosalind had said so at her colloquium in 1951, which Watson attended, but he had not understood.

JAMES WATSON: I cut some things out of cardboard and made the right shapes and pasted things on to indicate hydrogen atoms. The following morning, I started to put them together in pairs.

FRANCIS CRICK: In those days there was a brilliant young theoretical chemist in Cambridge, called John Griffiths. He died quite recently. One evening, we were sitting in a pub and talking about biological replication, and I said to him: perhaps the secret is that the bases attract each other in pairs, but like with like—adenine going with adenine, and guanine going with guanine? I met him, later, in the tea-queue at the Cavendish, and he told me he'd done a few scribbles on the back of an envelope and he'd found that it was not 'like with like', but that adenine stacked nicely on top of thymine, and guanine on top of cytosine. He'd been thinking along those lines at the time, but I didn't know that. The relative of the four bases in DNA had been worked out by a nucleic acid chemist called Erwin Chargaff, a few years before this time. It happened he was passing through Cambridge and he told us about his results, which were that the amount of adenine equalled the amount of thymine and the amount of guanine equalled the amount of cytosine in all sorts of DNA, wherever he looked, although the other ratios were all over the place. Anybody who knows about the history of science knows that when you have one-to-one ratios it means that things go together.

MICHAEL SWANN: The second clue came when Watson started playing with cardboard models of the bases. Watson suddenly saw that when A went with T, it formed the same shape pair as when C went together with G.

FRANCIS CRICK: Something came out of the model-building which Jim had done which he hadn't put in, and that's always the sign that you're on the right lines. Everything was finished except the hard work of producing an accurate model. Jim wasn't much good at that sort of thing, the models tended to flop about in his hands. I worked continuously for about four days, and then came the point where we saw that everything fitted, and I was so tired I went straight home to bed.

AARON KLUG: In Jim's mind, Pauling was the great rival but, in his rather perfunctory contacts with Rosalind, he hadn't got the measure of her at all. Indeed, he didn't know that she was only one or two steps away from the solution. But she didn't have a collaborator with whom she could discuss problems very closely, and she was one person against this powerful combination of two extraordinary people.

JAMES WATSON: Francis, do you think we were lucky, or was it real brain work?

FRANCIS CRICK: I guess we were certainly lucky, for two reasons. We were thinking about the problem at the right time, and then the two of us were collaborating: when one of us got on the wrong track, the other one got out of it. We weren't the least afraid of being very candid to each other, to the point of being rude, and if you don't have constant interchange, saying what you think of other people's ideas to their face, I don't think you can solve problems of this kind.

JAMES WATSON: If either of us had been two years older or two years younger, we would never have solved it. We had to be there just at that particular time.

FRANCIS CRICK: We pooled the way we looked at things. We didn't leave it that Jim did the biology and I did the physics. We both did it together, and switched roles and criticised each other, and this gave us a great advantage over the other people who were trying to solve it.

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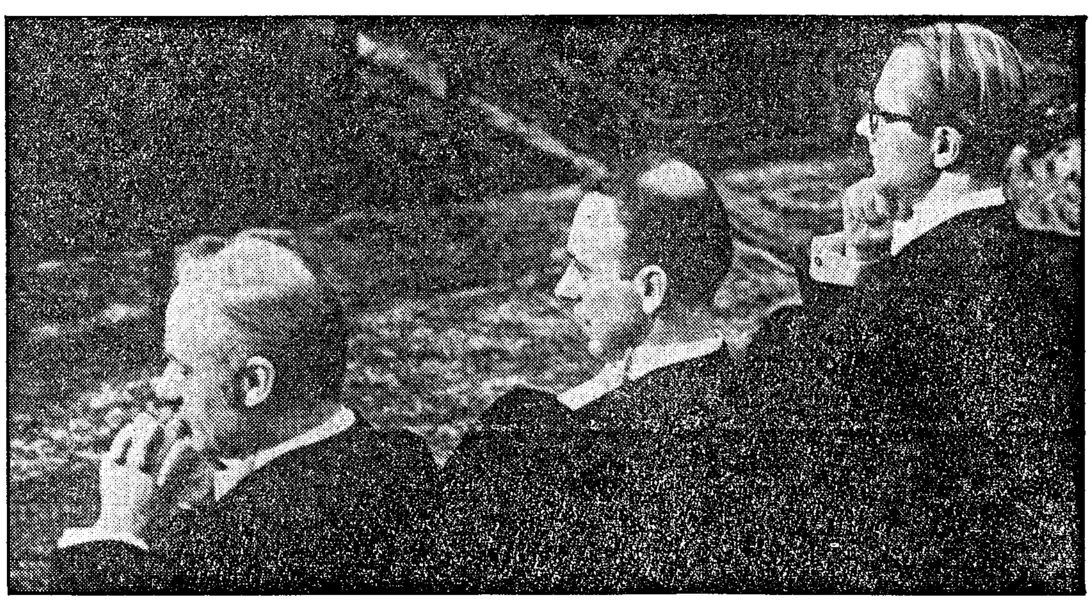

Nobel Prize winners: Francis Crick, James Watson, Maurice Wilkins